REMARKS

This paper is being presented in response to an official action dated October 10, 2001, wherein: **(a)** claims 1-62 were pending; **(b)** claims 19-29, 31, 59, and 60 have been withdrawn from consideration pursuant to the applicants' election on September 18, 2001; and, **(c)** the remaining claims — claims 1-18, 30, 32-58, 61, and 62 — have been rejected. Specifically, claims 18, 52-57, 59, and 61 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the recitation of "other somatoform disorders" and "related spectrum disorders." Claims 1-18, 30, 32-58, 61, and 62, to the extent that these claims read on the elected invention, have been rejected under 35 U.S.C. § 103(a) as being obvious over each of:

(A) Max and Kishore-Kumar et al., Biological Abstracts, Abstract No. 1991:300089 (1991);

(B) Max and Lynch et al., Biological Abstracts, Abstract No. 1992:330355 (1992);

(C) Max, Biological Abstracts, Abstract No. 1994:306038 (1994);

(D) Reimann et al., Chemical Abstracts, Vol. 121, Abstract No. 73757 (1994); and,

(E) Moore et al., Biological Abstracts, Abstract No. 1999:213502 (1999);

taken in view of:

(F) Dostert et al., PUBMED Abstract, PMID 9169308, UI: 97312867 (1997) ; and,

(G) Fleishaker *et al.*, *Biopharm. Drug Disp.* **20**:53-57 (1999).

Reconsideration and withdrawal of the rejections are requested.

This paper is timely-filed, as it is accompanied by a petition for a three-month extension of time, and the required extension fee.

The title of the application has been amended to be consistent with the claims.

Claims 1, 38, and 39 have been amended to recite methods of treating an individual suffering from chronic pain or methods of preventing an individual from having chronic pain by administration of a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, such as an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, wherein the optically pure (S,S) reboxetine is substantially free of (R,R) reboxetine. Support for the amendment to these claims can be found in the claims and specification of the application as filed, for example, in claims 18 and 30, and in the specification at page 18, line 30 to page 19, line 1.

Claims 18-31 and 41-62 have been canceled, without prejudice pursuant to the election made in a paper filed on September 18, 2001. Accordingly, by virtue of this amendment, claims 1-17 and 32-40 are pending.

Attached hereto (beginning at page 14) are sheets showing the changes made to the claims by this amendment. The attached sheets are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

The courteous interview granted by the examiner to the applicants' attorneys (James J. Napoli and Sandip H. Patel) and a representative (Dr. Stephen P. Arneric) of the assignee (Pharmacia & Upjohn Company) of the application on February 19, 2002, is hereby acknowledged with appreciation. The following remarks are presented in view of the issues discussed during that interview in an effort to resolve all outstanding issues and to lead to allowance of the application.

I. The 35 U.S.C. § 112, Second Paragraph, Rejection is Obviated

As noted above, claims 18, 52-57, 59, and 61 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the recitation of "other somatoform disorders" and "related spectrum disorders." Each of claims 18, 52-57, 59, and 61 has been canceled. Furthermore, the pending claims do not recite any of the offending terms (i.e., "other somatoform disorders" and "related spectrum disorders"). Accordingly, the foregoing claim amendments obviate the § 112, second paragraph, rejection and, therefore, reconsideration and withdrawal of the rejection are requested.

II. The 35 U.S.C. § 103(a) Rejection is Traversed.

As noted above, claims 1-18, 30, 32-58, 61, and 62, to the extent that these claims read on the elected invention, have been rejected under 35 U.S.C. § 103(a) as being obvious over each of the *abstracts* identified in **(A)** through **(F)** below (a complete citation to the abstracted article appears in brackets):

(A) Max and Kishore-Kumar et al., Biological Abstracts, Abstract No. 1991:300089 (1991) [Max *et al.* (1991) *Pain* **45**:3-10, hereafter the "1991 Max article"], which allegedly teaches that desipramine, amitriptyline, and other related antidepresants exhibit an analgesic effect by inhibiting reuptake of norepinephrine;

(B) Max and Lynch et al., Biological Abstracts, Abstract No. 1992:330355 (1992) [Max *et al.* (1992) *New Engl. J. Med.* **326**:1250-1256, hereafter the "1992 Max article"], which allegedly teaches that desipramine, a selective norepinephrine reuptake inhibitor, is effective at reducing pain caused by diabetic neuropathy;

(C) Max, Biological Abstracts, Abstract No. 1994:306038 (1994) [Max (1994) *Ann. Neurol.* **35**:s50-s53, hereafter the "1994 Max article"], which allegedly suggests that inhibiting reuptake of norepinephrine is the most important action accounting for pain relief;

(D) Reimann et al., Chemical Abstracts, Vol. 121, Abstract No. 73757 (1994) [Reimann *et al.* (1994) *Biochem. Pharmacol.* **47**:2289-2293, hereafter the "1994 Reimann article"], which allegedly teaches that tramadol exerts its analgesic effect by inhibiting reuptake of norepinephrine; and,

(E) Moore et al., Biological Abstracts, Abstract No. 1999:213502 (1999) [Moore *et al.* (1999) *Amer. J. Forensic Med. and Path.* **20**:98-100, hereafter the "1999 Moore article"], which allegedly teaches that tramadol exerts its analgesic effect by inhibiting reuptake of norepinephrine;

taken in view of:

(F) Dostert et al., PUBMED Abstract, PMID 9169308, UI: 97312867 (1997) [Dostert *et al.* (1997) *Euro. Neuropsychopharmacol* **7**:s23-s35, hereafter the

"1997 Dostert article"], which allegedly teaches that the (S,S) enantiomer of reboxetine is the more potent enantiomer; and,

(G) Fleishaker *et al.* (1999) *Biopharm. Drug Disp.* **20**:53-57, hereafter the "1999 Fleishaker article," which allegedly teaches that the (S,S) enantiomer of reboxetine is more potent in receptor binding and at inhibiting reuptake of norepinephrine.

Copies of the foregoing articles (A) through (F) are enclosed and identified in an information disclosure statement (IDS) filed concurrently herewith. A copy of the 1999 Fleishaker article was previously submitted with an IDS filed on August 14, 2000. Reconsideration and withdrawal of the § 103(a) rejections are requested.

According to the official action, the applied publications allegedly teach that norepinephrine reuptake inhibition is a biological mechanism for treating chronic pain and that the norepinephrine reuptake inhibitor (S,S) reboxetine is the more potent of the two enantiomers. (See page 4 of the October 10th official action.) Acccordingly (to the action), a person of ordinary skill in the art armed with this knowledge would have been motivated to treat chronic pain with optically pure (S,S) reboxetine. However, it appears that only the *abstracts* of publications **(A)** through **(F)** were reviewed in rendering the official action.

The obviousness rejections of the claims are premised on isolated statements taken from *abstracts* of the various publications that, when pieced together, might support the rejection. However, a close examination of the publications (and not merely the abstracts) and all that each discloses reveals that the isolated statements found in the abstracts do not reflect the teachings of the entire publication. Consequently, a person of ordinary skill in the art not cognizant of the teachings set forth in the instant application, would not discern from these publications the teachings the action alleges in support of the obviousness rejections. These publications do not contain the requisite objective teaching that would lead a person of ordinary skill in the art to the claimed invention. Specifically, these publications do not contain any objective teaching that highly selective inhibition of norepinephrine reuptake relieves chronic pain, such as pain caused by neuropathy. Thus, the pending claims are not rendered obvious by the prior art. *See Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985).

A. The Requirements of a § 103(a) Prima Facie Case of Obviousness

The U.S. Patent and Trademark Office (the "PTO") bears the burden of establishing a *prima facie* case of obviousness and "can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 5 U.S.P.Q.2d 1596, 1599-1600 (Fed. Cir. 1988). To support a conclusion that a claimed combination is obvious, either (a) the references must expressly or impliedly suggest the claimed combination to one of ordinary skill in the art, or (b) the PTO must present a convincing line of reasoning as to why one of ordinary skill in the art would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 U.S.P.Q. at 973. Where the teachings of various references conflict, the PTO must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 18 U.S.P.Q.2d 1089, 1091 (Fed. Cir. 1991).

B. No § 103(a) *Prima Facie* Case of Obviousness Exists

In general, the three applied Max articles (i.e., the 1991 Max article, the 1992 Max article, and the 1994 Max article) each disclose that a number of known antidepressants (i.e., amitriptyline, desipramine, imipramine, and clomipramine) are effective at blocking reuptake of norepinephrine and provide an analgesic effect to a patient suffering from pain caused by diabetic neuropathy. However, neither of these articles nor any of the other applied publications provide convincing evidence that such pain is reduced or eliminated *because* reuptake of norepinephrine is being blocked by administration of these antidepressants. When considered together, these Max articles certainly do not provide convincing evidence that highly selective inhibition of norepinephrine reuptake is the reason that pain caused by diabetic neuropathy is relieved. *See In re Young*, 18 U.S.P.Q.2d at 1091 (stating that the PTO must consider all disclosures in the prior art to the extent that the disclosures are in analogous fields of endeavor and, thus, would have been considered by persons having ordinary skill in the field of endeavor).

(i) The Combination of the 1991 Max Article in View of the 1997 Dostert Article and the 1999 Fleishaker Article Does Not Render the Claimed Invention Obvious

Specifically addressing the PTO obviousness rejections, the combination of the 1991 Max article in view of the 1997 Dostert article and the 1999 Fleishaker article does not render the claimed invention obvious. The 1991 Max article suggests (at pg. 8) that

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selective inhibition of norepinephrine reuptake is useful in treating pain caused by diabetic neuropathy, while also suggesting that selective inhibition of serotonin reuptake (by administration of paroxetine) is useful in treating the same pain. The 1997 Dostert article and 1999 Fleishaker article teach that reboxetine is a selective norepinephrine reuptake inhibitor, and that its (S,S) enantiomer is the more potent enantiomer. Because the 1991 Max article is inconclusive as to which mechanism is responsible for treating the pain, a person skilled in the art would not have been motivated to combine its teachings with those of the 1997 Dostert article and 1999 Fleishaker article to arrive at the claimed invention.

(ii) The Combination of the 1992 Max Article in View of the 1997 Dostert Article and the 1999 Fleishaker Article Does Not Render the Claimed Invention Obvious

The combination of the 1992 Max article in view of the 1997 Dostert article and the 1999 Fleishaker article does not render the claimed invention obvious. First, the 1992 Max article suggests (at pg. 1255) that selective inhibition of norepinephrine reuptake (by administration of amitriptyline or desipramine) is useful in treating pain caused by diabetic neuropathy, while also suggesting that selective inhibition of serotonin reuptake (by administration of paroxetine) is useful in treating the same pain. Second, the selectivity for norepinephrine over serotonin of desipramine (about 430) is much higher than that of amitriptyline (about 1.8). *See generally*, Owens *et al.* (1997) *J. Pharmacol. Exp. Ther.* **283**:1305-1322. If selective inhibition of norepinephrine were responsible for alleviating pain, then one would expect that desipramine would perform better than amitriptyline. However, the 1992 Max article concludes (at pg. 1253) that "[a]mitriptyline and desipramine reduced pain by similar amounts." Third, the 1992 Max article (at pg. 1255) concludes that "[o]ther mechanisms might contribute to the relief of pain," pointing out that both amitriptyline and desipramine block reuptake of other neurological receptors, such as histamine H_1, α_1-adrenergic, and muscarinic cholinergic. As previously noted, the 1997 Dostert article and 1999 Fleishaker article teach that reboxetine is a selective norepinephrine reuptake inhibitor, and that its (S,S) enantiomer is the more potent enantiomer. Because the 1992 Max article is inconclusive as to which mechanism is responsible for treating the pain, a person skilled in the art would not have been motivated to combine its teachings with those of the 1997 Dostert article and 1999 Fleishaker article to arrive at the claimed invention.

(iii) The Combination of the 1994 Max Article in View of the 1997 Dostert Article and the 1999 Fleishaker Article Does Not Render the Claimed Invention Obvious

The combination of the 1994 Max article in view of the 1997 Dostert article and the 1999 Fleishaker article does not render the claimed invention obvious. The 1994 Max article states (at pg. s51) that the "specific NE [norepinephrine] reuptake blocker desipramine appeared to approach the analgesic efficacy of the mixed NE/5HT [norepinephrine/serotonin] reuptake blocker amitriptyline." The 1994 Max article goes on to conclude (at pg. s51) that "there is some evidence of an edge for the mixed reuptake blockers." As noted above, the 1997 Dostert article and 1999 Fleishaker article teach that reboxetine is a selective norepinephrine reuptake inhibitor, and that its (S,S) enantiomer is the more potent enantiomer. Because the 1994 Max article is inconclusive as to which mechanism (if only one) is responsible for treating the pain, a person skilled in the art would not have been motivated to combine its teachings with those of the 1997 Dostert article and 1999 Fleishaker article to arrive at the claimed invention.

In general, a person of ordinary skill in the art would not be motivated to combine either of the Max articles with the 1997 Dostert article and 1999 Fleishaker article. The Max articles discuss the *selectivity* of various reuptake inhibitors (e.g., selectivity for serotonin over norepinephrine), whereas the 1997 Dostert article and 1999 Fleishaker article discuss the *potency* of compounds in receptor binding. Just because a compound is potent (or more potent) does not necessarily mean that the compound is selective (or more selective), or vice versa. Consequently, a person of ordinary skill in the art would not be motivated to use a potent compound in place of a selective compound, or vice versa, and reasonably expect the same results.

(iv) The Combination of the 1994 Reimann Article in View of the 1997 Dostert Article and the 1999 Fleishaker Article Does Not Render the Claimed Invention Obvious

The combination of the 1994 Reimann article in view of the 1997 Dostert article and the 1999 Fleishaker article does not render the claimed invention obvious. The 1994 Reimann article discloses (at pg. 2292) that tramadol is a centrally-acting analgesic and that it interferes with the noradrenaline uptake mechanism, especially when combined with desipramine, a known noradrenaline uptake inhibitor. Tramadol, however, is a mixed-receptor agonist and inhibits reuptake of other receptors, such as serotonin. (See the 1999 Moore article, at pg. 98.) As noted above, the 1997 Dostert article and 1999 Fleishaker article teach that reboxetine is a selective norepinephrine reuptake inhibitor, and that its (S,S)

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enantiomer is the more potent enantiomer. Because the 1994 Reimann article is inconclusive as to which mechanism is responsible for providing the analgesic effect, a person skilled in the art would not have been motivated to combine its teachings with those of the 1997 Dostert article and 1999 Fleishaker article to arrive at the claimed invention.

(v) The Combination of the 1999 Moore Article in View of the 1997 Dostert Article and the 1999 Fleishaker Article Does Not Render the Claimed Invention Obvious

The combination of the 1999 Moore article in view of the 1997 Dostert article and the 1999 Fleishaker article does not render the claimed invention obvious. The 1999 Moore article discloses (at pg. 98) that tramadol "has some affinity for the opiate receptors," and "is believed to exert [an] analgesic effect by inhibiting the reuptake of norepinephrine and serotonin." As noted above, the 1997 Dostert article and 1999 Fleishaker article teach that reboxetine is a selective norepinephrine reuptake inhibitor, and that its (S,S) enantiomer is the more potent enantiomer. Because the 1999 Moore article is inconclusive as to which mechanism is responsible for providing the analgesic effect, a person skilled in the art would not have been motivated to combine its teachings with those of the 1997 Dostert article and 1999 Fleishaker article to arrive at the claimed invention.

III. Unexpected Results and the Scope of Enablement

As amended, claim 1 is as follows:

> 1. A method of treating an individual suffering from chronic pain, the method comprising the step of administering to the individual a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000.

A. Unexpected Results

Filed concurrently herewith is a "Declaration of Stephen P. Arneric Pursuant to 37 C.F.R. § 1.132" (the "Arneric Declaration"). Paragraphs 8-11 of the Arneric Declaration and Tables I and II attached thereto relate to inhibition constants of compounds for various monoamine transporter and receptor sites, and the selectivity of the compounds for the norepinephrine transporter site over the serotonin transporter site.

As reported in Table II, desipramine exhibits selectivity (430 fold) for the norepinephrine transporter site over that of the serotonin transporter site. In the 1991 Max article, Max et al. have suggested that blockade of norepinephrine reuptake, an action shared by desipramine, amitriptyline, and other antidepressants proven effective in neuropathic pain, may mediate the pain relief. In their study, Max et al. demonstrate the effective plasma levels required to produce pain relief in a majority of patients (13 of 18, or 72%) is in the range of 50 to 150 ng/ml. (See Figure 4 at p. 7 of the Max 1991 article.) This translates to a total plasma concentration of 188 to 540 nM, or approximately 9 to 28 nM, if one were to correct for the portion of free drug available to associate with the receptor, knowing the other portion is bound to plasma proteins. Based on Figure 4 of the Max 1991 article, there is a reasonable probability that a significant portion (approximately 50%) of the H_1 and α_1-adrenergic receptors would also be occupied at plasma concentrations that produce relief from neuropathic pain. Consequently, one cannot definitively conclude that desipramine produces relief from neuropathic pain by interacting solely at the norepinephrine transporter site. Consequently, one cannot definitively conclude that desipramine produces relief from chronic pain solely through its interaction with the norepinephrine transporter site. (See Arneric Declaration at ¶ 9.)

The data reported in Tables I and II for (S,S) reboxetine stand in stark contrast to the corresponding data for desipramine. Specifically, (S,S) reboxetine exhibits surprisingly exceptional selectivity (>15,000) for the norepinephrine transporter over that of the serotonin transporter. See Table II. Consequently, and in contrast to desipramine, one can definitively conclude that compounds, such as (S,S) reboxetine, produce relief from chronic pain solely through their highly selective interaction with the norepinephrine transporter site. (See Arneric Declaration at ¶ 10.)

Still further, the data reported in Table I conclusively shows that (S,S) reboxetine is a highly selective inhibitor of the norepinephrine transporter site having almost 25,000 fold selective response over other transporter/receptor sites (5-HT_{2A}, H_1, α_1-adrenergic, and muscarinic) believed to be responsible for adverse side effects. Such high selectivity is not exhibited by any of the comparative compounds. Thus, the selectivity of compounds, such as (S,S) reboxetine, should provide an overall improved safety and tolerability far beyond that of conventional tricyclic antidepressants. (See Arneric Declaration at ¶ 11.)

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It is respectfully submitted, that the unexpected results/findings (e.g., compounds having selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000 versus comparative compounds, such as desipramine, for example, which has a selectivity of 430) provide evidence of non-obviousness.

B. Scope of Enablement

Paragraphs 13 and 14 of the Arneric Declaration describe techniques and assays used to determine inhibition constants of compounds for various monoamine transporter and receptor sites. Paragraphs 15-18 of the Arneric Declaration establish that such techniques and assays are standard in the art and amendable to high throughput screening.

Specifically, these techniques and assays are amenable to high throughput screening (HTS) technologies that use robotics to automate handling and dilutions of compounds, and can be performed by one skilled in the art of HTS to identify compounds with potential for phramaceutical applications. (See Arneric Declaration at ¶ 16.)

Although it was surprising and unexpected that (S,S) reboxetine exhibits remarkably greater selectivity for the norepinephrine transporter than it does for the serotonin transporter, it would be possible to search for such compounds using HTS technologies without undue experimentation. (See Arneric Declaration at ¶ 17.)

Furthermore, it is entirely conceivable that up to 500,000 novel compounds could be screened within a three-month time period for their ability to selectively interact with the norepinephrine transporter. One such HTS screening process could be performed at a single concentration (1 μM) and examine the ability of the screening compound to displace [N-methyl-^{3}H]-nisoxetine, a relatively selective ligand for the norepinephrine transporter, from rat brain membrane preparations. Compounds found to be active would be confirmed by completeing a full concentration-response curve, and the initial selectivity against the serotonin transporter would be confirmed using [N-methyl-^{3}H]-citalopram, a relatively selective serotonin ligand. The functional nature of these interactions with human recombinant norepinephrine, serotonin, and DAT transporter sites could be confirmed in secondary screening assays. (See Arneric Declaration at ¶ 18.)

It is respectfully submitted that one of ordinary skill in the art, using the standard techniques and assays with HTS, can readily determine whether a compound falls

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within the scope of the pending claims, without undue experimentation. Consequently, the scope of the pending claims is properly enabled under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In summary, the applicants respectfully request: **(a)** cancellation of claims 18-31 and 41-62; **(b)** entry of the amendments to claims 1, 38, and 39; **(c)** reconsideration and withdrawal of all of the rejections of the claims; and, **(d)** allowance of all claims pending after entry of the foregoing amendments (*i.e.*, claims 1-17 and 32-40).

Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, he is urged to contact the undersigned attorney.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

March 25, 2002 By

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the title as follows:

[HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS AND METHODS OF USING THE SAME] METHOD OF TREATING OR PREVENTING CHRONIC PAIN WITH A HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITOR

In the Claims:

Please amend claim 1 as follows:

1. A method of [selectively inhibiting reuptake of norepinephrine,] treating an individual suffering from chronic pain, the method comprising the step of administering to the individual a therapeutically effective amount of a composition [to an individual, the composition] comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000.

Please cancel claims 18-31, without prejudice.

Please amend claims 38 and 39 as follows:

38. A method of [treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit,] preventing an individual from having chronic pain, the method comprising the step of administering to the individual a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000.

39. A method of treating [a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit,] treating an individual suffering from chronic pain while diminishing adverse side effects, the method comprising the step of administering to the individual a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

thereof, [to an individual,] said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

Please cancel claims 41-62, without prejudice.